JBP 246
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Charles E. Clum et al.

Serial No.: 700,165 Group No.: 125

Filed : February 11, 1985 Examiner : J. Lipovsky

For : SKIN CARE COMPOSITIONS

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D. C. 20231 on November 20, 1986
(Date of Deposit)
Steven P. Berman
Name of applicant, assignee, or Registered Representative
Steven P. Berman
(Signature)
11/20/86
(Date of Signature)

87-2039

APPELLANTS' BRIEF ON APPEAL UNDER 37 C.F.R. 1.192

Honorable Commissioner of Patents and Trademarks
Washington, D. C. 20231

Dear Sir:

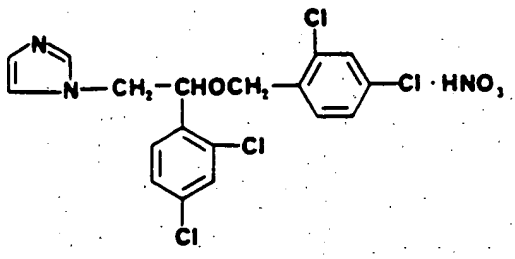
This is an appeal from the decision of the Primary Examiner dated May 28, 1986 rejecting Claims 1 and 4-6 and the Advisory Action dated September 15, 1986 still holding the above-identified claims not allowable.

A request and authorization to charge the Deposit Account of Johnson & Johnson, Account No. 10-750, the amount of $130.00 as the requisite fee is enclosed (in duplicate). An oral hearing is requested.

CLAIMS ON APPEAL

1. A skin care composition comprising as the active components

(a) miconazole nitrate of the formula



and

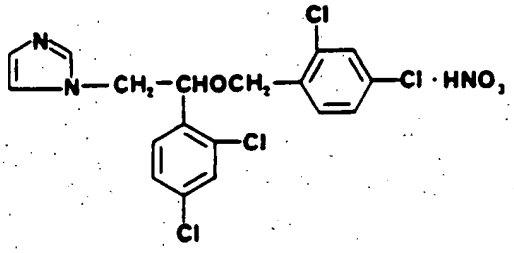
(b) zinc oxide;

wherein the miconazole nitrate and zinc oxide are present in a ratio of from about 1:60 to about 1:333.

4. The composition of Claim 1 wherein the miconazole nitrate and zinc oxide are present in a ratio of about 1:60.

5. A method for treating diaper rash comprising applying to the affected skin area a composition containing an antimicrobially effective amount of

(a) miconazole nitrate of the formula



and

(b) zinc oxide;

wherein the miconazole nitrate and zinc oxide are present in a ratio of from about 1:60 to about 1:333.

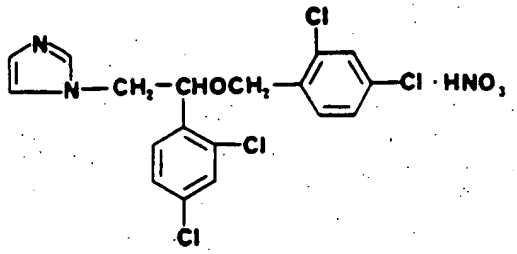
6. The method of Claim 5 wherein the miconazole nitrate and zinc oxide are present in a ratio of about 1:60.

SUMMARY OF THE INVENTION

This invention relates to skin care compositions and more particularly to skin care compositions which can be applied topically to prevent or treat acute inflammatory skin conditions, especially in young children.

One of the most prevalent inflammatory skin conditions to afflict infants and young children is "diaper rash". Diaper rash is an acute, superficial inflammatory dermatitis which is frequent during the diaper wearing period. It is characterized by maceration, chaffing and erythematosis papules, and the skin is sensitive and painful to the touch. The sites of inflammation are normally the buttocks, groin, inner thighs and the folds of joints. In severe cases, the inflammation is complicated by infection with one or more of the indigenous saprophytic microorganisms which are present in the diaper areas notably bacteria such as Staphylococcus aureus or yeast such as Candida albicans. Over the years, numerous methods of prevention and treatment of diaper rash have been advocated with varying degrees of success.

The present invention comprises a synergistic combination of a specific imidazole derivative and zinc oxide in claimed ratios of from about 1:60 to about 1:333. The specific imidazole derivative useful in the present invention is miconazole nitrate of the formula



The synergistic efficacy of the compositions of the present invention were demonstrated in vivo and in vitro in Examples VI and VII and Tables I-IV of the specification as well as in the additional data submitted in Declarations under Rule 132, all of which will be discussed in detail hereinafter.

THE PRIOR ART

The following reference was cited in the Final Rejection of the application:

Schmidt-Ruppin et al., U.S. Patent No. 4,318,926, 3/1982

The Schmidt-Ruppin et al. reference discloses a method of treating herpes infections by administering anthracene-type compounds and compositions containing same.

THE FINAL REJECTION

Claims 1 and 4-6 were rejected under 35 U.S.C. 103 as being unpatentable over Schmidt-Ruppin et al. for "reasons already made of record in the previous Office Action". In said

previous Office Action, it was stated that Schmidt-Ruppin et al. "teach the use of topical creams and ointments containing zinc oxide (col. 8, lines 30-34) which may additionally contain biologically active substances including miconazole (col. 8, line 77 - col. 9, line 15). The determination of both optimal proportions and target use are matters of obvious alternative to one with skill in the art". It was further stated in the Final Rejection that "Applicants' arguments and declarations have been considered but are not found to be convincing with regard to the presently claimed scope". In the Advisory Action, it was stated that "The data in the specification and the newly submitted affidavits taken as a whole do not substantiate the allegations of synergism regarding a miconazole nitrate:zinc oxide ratio of 1:60. Upon appeal, the claims stand rejected for reasons already of record.".

APPELLANTS ARGUMENTS AND AUTHORITIES

The Schmidt-Ruppin et al. reference discloses a method of treating herpes infections by administering anthracene-type compounds and compositions containing same. These anthracene compounds act upon the central nervous system, and it is alleged thereby combat herpes infections. In column 7, line 43 of the reference, it indicates that pharmaceutical preparations containing these anthracene actives for topical use can be in the form of creams, ointments, gels, vaginal-ovula, pastes, foams, tinctures and solutions; and in column 8, line 30 et seq., it further indicates that pastes are creams and ointments having secretion-absorbing powder constituents such as metal oxides, including zinc oxide. It also states that biologically active substances including miconazole can be added to these compositions.

Appellants respectfully contend that the teachings and disclosures of the Schmidt-Ruppin et al. reference would neither teach nor suggest to one skilled in the art the present invention. To contend that from a teaching of utilizing anthracene-type actives to act upon the central nervous system one skilled in the art would arrive at the present invention is not reasonable. To obtain Appellants' compositions from this reference, one would have to formulate the composition containing the anthracene compound in a cream form utilizing zinc oxide and add thereto miconazole and then delete the anthracene active and adjust the ratios of the remaining components. Such is clearly not obvious from the teachings of the Schmidt-Ruppin et al reference.

The compositions of the present invention are limited to skin care compositions containing miconazole nitrate and zinc oxide in specific ratios which exhibit synergistic interaction. There is no intent whatsoever of including systemically active compounds such as the anthracene compounds disclosed in the reference, and the Examiner's reliance on this reference is considered inappropriate in view of the teachings therein. It is respectfully submitted that in attempting to maintain a rejection based on 35 U.S.C. 103, the Examiner has drawn incorrect conclusions not justifiable in view of the teachings of the cited art.

More than mere allegations are necessary to substantiate a rejection under 35 U.S.C. 103. As a CCPA stated in In Re Warner, 114, U.S.P.Q. 173 at 178 (CCPA 1967):

"A rejection based on Section 103 clearly must rest on a factual basis, and these facts must be interpreted without hindsight reconstruction of the invention from the prior art. In making this evaluation, all facts must be considered. The Patent Office has the initial duty of supplying the factual basis for its rejection. It may not, because it may doubt that the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in its factual basis. To the extent the Patent Office rulings are so supported, there is no basis for resolving doubts against their correctness. Likewise, we may not resolve doubts in favor of the Patent Office determination when there are deficiencies in the records as to the necessary factual basis supporting its legal conclusion of obviousness."

It is respectfully contended that the Examiner has not satisfied the burden of basing a rejection under 35 U.S.C. 103 on a factual basis.

Support for Appellants' claimed synergistic compositions with specific ratios of miconazole nitrate to zinc oxide of from about 1:60 to 1:333 can be found in the specification and examples as well as in the Declarations under Rule 132 submitted during the prosecution of the application.

In Example VI of the specification (page 9) and as amplified in the Declarations Under Rule 132 of Dr. James J. Leyden (March 17, 1986) and Dr. Bruce Semple (March 7, 1986 and August 27, 1986), the following in-vivo test procedure was carried out by Dr. Leyden to demonstrate the synergism and efficacy of compositions containing miconazole nitrate and zinc oxide in a ratio of about 1:60.

Ten subjects (four females and six males) with an age range of 19 to 27 years were randomized into a controlled double-blind study to compare the ability of four treatments to prophylactically inhibit the growth of Candida albicans on the

arms of the subjects. Six test sites on the forearms of each subject were randomized according to the following treatment plan:

a) Base (no actives)
b) 15% zinc oxide in base
c) 0.25 miconazole nitrate in base
d) 0.25 miconazole nitrate and 15% zinc oxide (1:60 ratio) in base
e) no treatment

Twenty microliters of a saline suspension of Candida albicans containing 1 million cells per milliliter are applied to three one square centimeter test sites on the volar forearm surface of each volunteer subject. The areas are covered with an impermeable plastic film and secured with tape. The test sites are uncovered six hours after inoculation and treated with one of the test products or left untreated as a control. The sites are then redressed with plastic film for an additional 24 hours. The test products are then removed from all sites and cultures are obtained by the standard detergent scrub method of Williamson and Kligman. This method is set forth in the Journal of Investigative Dermatology, Vol. 45, No. 6, pps. 498-503 (1965).

Two different types of measurements and data were obtained from these tests; microbiological measurements and clinical measurements. The microbiological data was obtained as follows: cultures from all test sites collected as above were prepared on Trypticase Soy Agar and Littman Media plates and incubated for 48 hours. Colonies were then counted by standard

microbiological methods. For each of the counts, miconazole alone gave lower counts than zinc oxide alone, but these difference were not statistically significant. For Candida albicans on Trypticase media, miconazole alone gave lower counts than the base, while the remaining products do not differ. For Candida albicans on Littman media, counts with miconazole alone and zinc oxide alone were lower than the base, but not different from each other or the untreated site. Results for the miconazole nitrate and zinc oxide product were significantly lower than all the other products. To determine if the relation between zinc oxide and miconazole was additive or synergistic, a second analysis of variance was performed without the untreated site. The model included zinc oxide, miconazole and the interaction of these ingredients. The results show a small but statistically significant synergistic effect and these microbiological results can also be represented in tabular form as follows:

Synergistic Activity of Zinc Oxide on Miconazole Nitrate
Inhibition of the Growth of Candida Albicans at
Miconazole Nitrate Concentration of 0.025 w/v

Zinc Oxide Concentration 15% w/v	Inhibition for Miconazole Nitrate (%)	Inhibition for Zinc Oxide (%)	Sum of Components %	Inhibition for Combination %
Trypticase Media	13.8	5.5	19.3	25.0
Littman Media	15.4	7.6	23.0	25.0

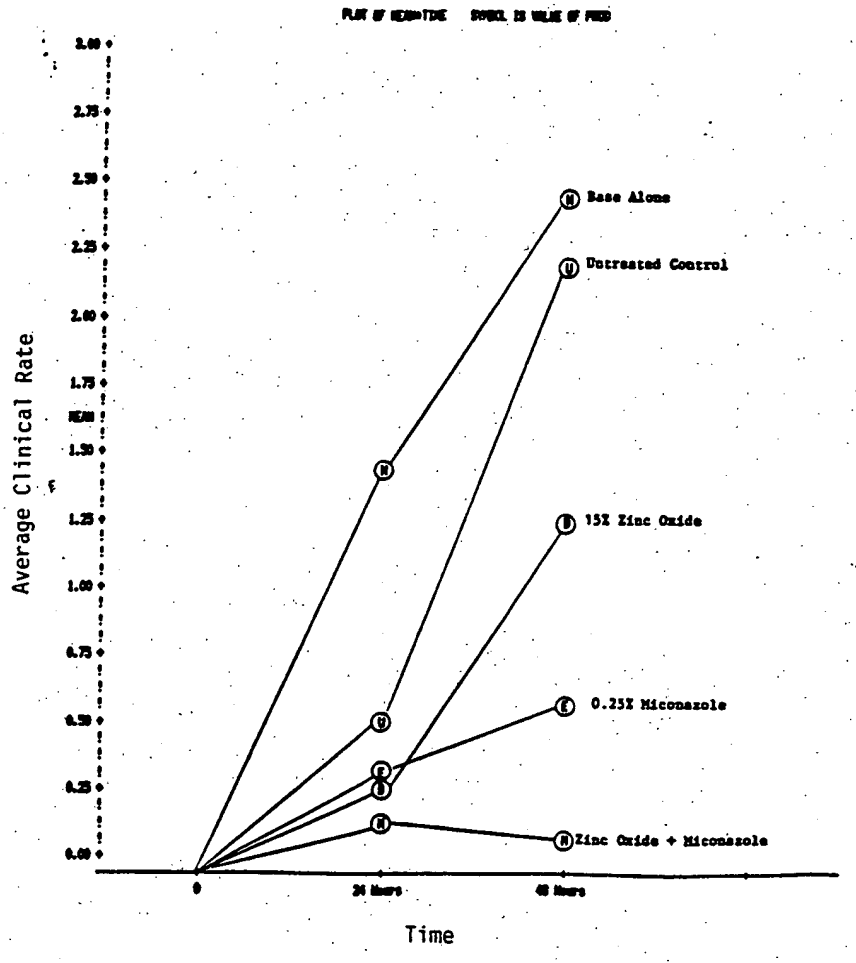
These results exhibit a statistically significant synergistic effect. This synergistic effect cannot be attributed to experimental error because of the precision of the experiment itself and particularly the microbiological counts. The probability of an experimental error producing this effect is $p<0.05$. Therefore, the inhibition for the combination, i.e., miconazole nitrate and zinc oxide, in both the Trypticase media and the Littman media demonstrates synergism.

The clinical data was obtained as follows: measurements were obtained by experienced investigators for each site immediately prior to treatment, at 24 hours and at 48 hours after treatment. Grading is done on a scale of 0=no reaction, 1=minute pinpoint papules and/or faint erythema, 2=at least 5 discrete papules or pustules and definite erythema, 3=greater than 10 papules or pustules and erythema, 4=confluent papules or pustules and intense erythema. The following clinical results were obtained: at 24 hours, reactions at the sites treated with base only were more severe than the other treatments, while the other products did not differ significantly. By 48 hours, the clinical severity had increased with all treatments except the zinc oxide-miconazole product. The zinc oxide-miconazole product severity was directionally less than miconazole alone, and significantly less than all other treatments both by chisquare tests and two-way analysis of variance.

One could reasonably conclude from these tests that the clinical scores 48 hours after inoculation demonstrated that the combination of miconazole nitrate and zinc oxide was

superior to miconazole alone and superior to the other treatments. Furthermore, the combination produced significantly lower counts of Candida albicans than all other treatments.

These clinical results can be represented in graphical format as follows:



These results clearly demonstrate, both clinically and microbiologically, that the combination of miconazole nitrate and zinc oxide in a 1:60 ratio is superior to miconazole nitrate alone and also has a synergistic effect. The results are statistically and clinically significant, especially when based on the experience of an investigator of the renown of Dr. James Leyden. As is clearly evident from his Declaration Under Rule 132, Dr. Leyden is a world renown clinical dermatologist. He is a full Professor of Dermatology at the University of Pennsylvania School of Medicine and serves as a consultant to the U.S. Food & Drug Administration and the U.S. Federal Trade Commission as well as the drug regulatory agencies of Canada, United Kingdom, Germany and Australia. He has authored or co-authorized over 160 articles and 33 books, chapters or reviews. He has also received various awards including in 1985 the Gold Award for Original Investigation by the American Academy of Dermatology.

It is respectfully contended that as a result of the nature of the tests, the results therefrom and the individual who directed same, that these tests clearly substantiate the claim of synergism of miconazole nitrate and zinc oxide on a ratio of about 1:60 against Candida albicans.

In Example VII of the specification and as amplified in the Declaration Under Rule 132 of Dr. David M. Isaacson (March 10, 1986), a qualitative in vitro test procedure was carried out by Dr. Isaacson to demonstrate the synergism of compositions containing miconazole nitrate and zinc oxide.

The test procedure consisted of preparing weighed suspensions of zinc oxide and/or miconazole nitrate in measured volumes of melted microbial growth supporting agars. Aliquots of these agar suspensions were transferred to petri plates and allowed to solidify. During the solidifying process, the zinc oxide and/or miconazole nitrate particles were maintained in suspension in the agar in the petri plates by imparting constant motion to the plates positioned on a reciprocating or rotary platform shaker. To the surface of the solidified agar suspension was added 0.02 ml of inoculum of S. aureus containing approximately 300 colony forming units (CFU) of microbial suspension (1.5×10^4 CFU/ml). The organisms were then distributed evenly over the agar surface with a sterile glass spreader. The plates were then incubated 2 to 4 days at $35^{\circ}C$. After the incubation period, the plates were examined for evidence of growth inhibition by determining the presence or absence of surface colonies. The number of colonies on each plate at each concentration of miconazole nitrate alone was noted. Similarly the number of colonies was noted on each plate at each concentration of zinc oxide alone, and on plates containing combinations of different concentrations of both miconazole nitrate and zinc oxide. The "percent inhibition" of the bacteria produced at a particular concentration of miconazole nitrate alone was calculated by comparing the number of colonies obtained at that concentration with the number of colonies of the negative control plate containing no zinc oxide or miconazole nitrate. Similarly, the "percent inhibition" produced at one concentration of zinc oxide alone was calculated by comparing the number of colonies obtained at that concentration of zinc oxide with the number of colonies

produced on the negative control plates containing no miconazole nitrate or zinc oxide. To determine the effect of zinc oxide on miconazole nitrate activity, the "percent inhibition" of the organisms in contact with any of the combinations of zinc oxide and miconazole nitrate concentrations were calculated by relating the number of surviving colonies on the agar surface of those plates with the number of surviving colonies on the base line control plates containing the same concentration of zinc oxide alone. These results are expressed as percent inhibition of the organism at a specific concentration of miconazole nitrate alone (Inhibition for Miconazole); as percent inhibition of the organism at a specific concentration of zinc oxide alone (Inhibition for Zinc Oxide); as the percent inhibition expected if the inhibition obtained for miconazole nitrate and for zinc oxide were additive (Sum of Components), and as the observed inhibition at specific concentrations of zinc oxide and miconazole nitrate (Inhibition for Combination).

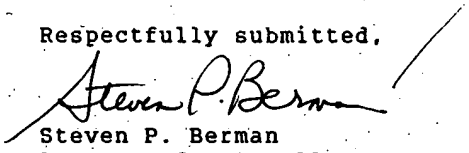
The results in the specification and the results reported in the Declaration clearly demonstrate the synergistic activity of combinations of miconazole nitrate and zinc oxide in a 1:60 ratio against Staphylococcus aureus and exhibit synergistic activity against Staphylococcus aureus in ratios of from about 1:60 to 1:333; and together with the data generated by Dr. Leyden clearly demonstrate that combinations of miconazole nitrate and zinc oxide exhibit synergistic activity against Candida albicans in ratios of from about 1:60 to 1:333.

SUMMARY

Therefore, Appellants respectfully contend that in no way does the cited prior art teach or suggest to one skilled in the art the present invention. Furthermore, Appellants respectfully contend that the data contained in the specifications as amplified by the Declarations Under Rule 132 support claims directed to compositions containing miconazole nitrate and zinc oxide in ratios of from about 1:60 to 1:333.

Appellants therefore respectfully request that the rejection under 35 U.S.C. 103 be reversed by this Board and that Claims 1 and 4-6 be deemed allowed.

Respectfully submitted,



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